AD_____

AWARD NUMBER DAMD17-98-1-8331

TITLE: Ultrasonic Morphological Analyzers for Breast Cancer Diagnosis

PRINCIPAL INVESTIGATOR: Frederic L. Lizzi, Eng.Sc.D.

CONTRACTING ORGANIZATION: Riverside Research Institute
New York, New York 10036-6991

REPORT DATE: July 1999

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	July 1999	Annual (1 Jul 98 - 30 Jun 99)

4. TITLE AND SUBTITLE
Ultrasonic Morphological Analyzers for Breast Cancer Diagnosis

5. FUNDING NUMBERS
DAMD17-98-1-8331

6. AUTHOR(S)
Frederic L. Lizzi, Eng.Sc.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Riverside Research Institute
New York, New York 10036-6991

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

The goal of this research is to improve ultrasonic classification of breast lesions and guide decisions regarding biopsy requirements, especially for small lesions and those in young, dense breasts, which are particularly difficult to evaluate with mammography. The research is developing a set of complementary ultrasonic morphological analysis procedures (UMAPs) that analyze digital ultrasonic echo data. Each UMAP extracts a particular quantitative lesion feature that is now subjectively described; these include "echogenicity," "heterogeneity," "shadowing," and lesion boundary characteristics. The set of complementary UMAP features will be analyzed with statistical procedures to derive reliable and objective lesion classification.

UMAP processing is being applied to digitized radio-frequency echo data previously acquired in 140 clinical breast examinations with linear-array ultrasound systems. Anonymous ancillary patient data (including reports from subsequent biopsies) and system calibration data are stored in archival data files. Also stored are the clinicians' levels-of-suspicion that a lesion is cancerous; these LOS values were based on conventional, subjective scoring of ultrasonograms.

After refining each UMAP procedure, lesion classification will be evaluated using multi-parameter discriminant functions. To quantify incremental benefits for breast cancer identification, ROC curves for UMAP classification will be compared to ROC curves based on the clinicians' LOS that a lesion is cancerous.

14. SUBJECT TERMS
Breast Cancer, Ultrasound, Ultrasonic Spectrum Analysis, Breast Lesion Classification

15. NUMBER OF PAGES
10

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

____ Where copyrighted material is quoted, permission has been obtained to use such material.

____ Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

____ Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

____ In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and use of Laboratory Animals of the Institute of Laboratory Resources, national Research Council (NIH Publication No. 86-23, Revised 1985).

__✓__ For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

____ In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

____ In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

____ In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

Frederic L Lizzi — July 28, 1999

PI - Signature — Date

(4) TABLE OF CONTENTS

(5) INTRODUCTION

The goal of this research is to improve ultrasonic classification of breast lesions and guide decisions regarding biopsy requirements, especially for small lesions and those in young, dense breasts, which are particularly difficult to evaluate with mammography. The research is designed to go beyond current capabilities by developing a set of complementary ultrasonic morphological analysis procedures (UMAPs) that analyze digital ultrasonic echo data. Each UMAP is optimized for extracting a particular quantitative lesion feature that describes the spatial configuration or acoustic properties of the lesion. The set of complementary UMAP features will be analyzed with statistical procedures to derive reliable and objective lesion classification for use in patient management.

(6) BODY OF ANNUAL SUMMARY

The research conducted during the first year of this program addressed issues itemized in the Statement of Work of our proposal. The research is planned to derive quantitative UMAP evaluations of features that are now subjectively described; these include "echogenicity," "heterogeneity," "shadowing," and lesion boundary characteristics. Progress during this report period will be described in terms of the constituent steps needed to evaluate our concepts. These include: ultrasonic parameter imaging; region-of-interest definition; implementation of complementary UMAP techniques; and, initial classification efforts.

During this report period, we developed quantitative ultrasonic parameter imaging techniques to process original digital data and display cross-sectional images of B-mode ultrasonograms and selected ultrasonic spectral parameters. The clinical data being processed was obtained previously at three clinical sites using ATL Ultramark 9 systems with linear L10-5 arrays. Data sets include digitized radio-frequency (RF) echo data acquired at the transducer, before any conventional processing was applied. Calibration signals from each system are also stored for use in removing system-dependent signal artifacts. Complete clinical records (including subsequent biopsy reports) are stored anonymously for each of 40 biopsy-proven cancerous lesions and more than 100 biopsy-proven non-cancerous lesions. Also stored are the clinicians' level-of-suspicion that each lesion was cancerous; these levels were based on standard interpretation schemes applied to conventional ultrasonograms. Digitized RF data records were obtained for several complete scans of each lesion as well as ultrasonic scans of the contralateral breast.

The new digital algorithms we developed during this report period use MATLAB applications for generating cross-sectional tissue images. For B-mode imaging, stored time-gain-control (TGC) data are used to compensate for operator settings and overall system gain. Stored RF data are processed with an analytic-signal-magnitude routine to obtain high-quality video signals, which are employed for B-mode images.

During this period, we implemented and tested spectral processing techniques that involve a sequence of procedures to compute and display frequency-dependent features of tissue backscatter. After TGC compensation, RF echoes along each scan line are analyzed with a sliding 64-point Fourier Transform algorithm (incorporating a Hamming weighting function). At each location spectral amplitudes are computed in dB over a selected frequency range (5 - 9 MHz). To extract summary spectral features, linear regression is applied to compute the spectral intercept (dB; extrapolation to zero frequency) and midband fit (dB; value of the regression line at the center frequency).

Local intercept and midband fit values are next calibrated with respect to an absolute

reference level, using stored calibration data obtained for each clinical system. Our processing includes two calibration procedures. The first removes frequency characteristics of the transducer and pulser-receiver; here, relevant data were obtained with planar focal-plane reflectors. The second procedure removes range and frequency effects of ultrasonic diffraction; relevant calibration data were obtained with rubber blocks embedded with diffuse distributions of 10-μm glass spheres.

The final result of these procedures is a set of images and files containing corresponding values of: B-mode (video) signals; intercept values; and, midband fit values.

During this period, the above procedures were all implemented and tested on clinical data using MATLAB. We also developed region-of-interest (ROI) procedures using algorithms that can be applied to any of the above image types. As described below, medical personnel must identify several types of ROI's in each scan plane; thus, we developed simple user-interfaces to define, review, and edit manually selected ROI's. The ROI's include: lesion boundaries; anterior segments (directly anterior to and lateral to the lesion); similar segments posterior to the lesion; lateral regions on either side of the lesion; and, the breast surface (for cases where stand-off coupling pads were used during scanning).

After developing the above imaging and ROI algorithms, we implemented processing software for key UMAP functions. The following measurements were implemented:

1) "Echogenicity": This is now computed as the mean spectral intercept value within the outlined lesion boundary. Intercept was selected for this measure because it is not affected by typical attenuation losses in intervening tissues.

2) "Heterogeneity": This is now computed as the standard deviation of the spectral midband fit within the lesion. We also implemented several alternative measures of statistical dispersion for study during the remainder of this program. Midband fit values were chosen for this measure since they can be estimated with higher precision than other spectral descriptors.

3) "Shadowing": This parameter measures the attenuation in lesions relative to the attenuation in surrounding tissues. We have implemented software that quantitatively estimates lesion attenuation coefficients by computing the difference between midband fit values in shadowed regions (directly posterior to the lesion) and values in similar unshadowed regions (laterally displaced from shadowed regions). The computation accounts for lesion thickness, determined from the traced lesion boundary.

To complement these features, we have now started to examine a number of procedures to quantitatively characterize lesion-boundary features such as lobulation and eccentricity.

We have tested and refined the above spectral measurements on a selected subset of clinical cases. The current UMAP feature set, augmented by lesion-boundary features and comparisons with contralateral-breast features, will be applied to the entire set of clinical data during the next program-year. Classification will be quantified using discriminant analysis and Receiver Operator Characteristics (ROC). To determine incremental benefits for identifying cancerous lesions, we will compare ROC curves for UMAP classification with ROC curves for clinicians' level-of-suspicion (based on conventional ultrasonic interpretation schemes).

(7) SUMMARY APPENDICES

1) List of key research accomplishments

- implementation of software for computing, calibrating, and displaying ultrasonic spectral features of breast tissues
- implementation of software and simple user-interface for defining breast lesions and relevant regions-of-interest
- implementation and testing of software for lesion feature extraction including quantitative measures of:
  - echogenicity
  - heterogeneity
  - attenuation
- initial specification of techniques to quantify the spatial configurations of lesions
- initial testing of concepts on selected cases preparatory to comprehensive application to all cases and statistical evaluation of lesion identification, to be performed during the following period.

2) List of reportable outcomes

"Ultrasonic spectrum analysis procedures for breast cancer classification," S.K. Alam, F.L. Lizzi, E.J. Feleppa, T. Liu and A. Kalisz, 24th International Symposium on Ultrasonic Imaging and Tissue Characterization, Arlington, VA, June 2-4, 1998.

Several additional abstracts and manuscripts are in preparation or review.

3) Copy of abstract (on following page)

Ultrasonic spectrum analysis procedures for breast cancer classification

S.K. Alam, F.L. Lizzi, E.J. Feleppa, T. Liu and A. Kalisz

Riverside Research Institute, 330 West 42nd Street, New York, NY 10036

We have developed a series of spectrum analysis procedures designed to quantify ultrasonic breast cancer evaluations. The procedures have been planned to improve upon B-mode differentiation of benign and malignant lesions, which employs features such as "echogenicity," "heterogeneity," and "shadowing." Our goal is to replace each of these subjective features with corresponding quantitative parameters based on spectrum analysis of radio-frequency (RF) echo signals in order to remove operator dependence and to permit objective discrimination.

Our technique involves an image-based approach to calibrated spectrum analysis. This has been implemented using RF data digitally acquired from several clinical sites using an ATL Ultramark 9 system. The first step is the digital synthesis of spectral-parameter images derived with sliding-window Fourier transform techniques, as described in previous reports for other organs. Images of uncalibrated local values of spectral intercept and midband fit are generated using a new MATLAB® (The MathWorks, Inc., Natick, MA) implementation. These quantitative images are then calibrated using the spectrum of a planar target together with a range-dependent diffraction correction for each parameter. Diffraction correction employs power spectra measured from diffuse scatterers in a gel or rubber block; it depends upon the specific transducer array and transmit focal-length used in each examination.

Classification parameters are derived after tracing the boundary of breast lesions on midband fit images; each parameter replaces a specific B-mode descriptor. "Echogenicity" is measured as the mean spectral intercept within the lesion, since this value is not significantly affected by frequency-dependent attenuation in intervening media. "Heterogeneity" is measured as the statistical dispersion of midband fit values within the lesion. This definition is motivated by previous analysis that demonstrated how the histogram of midband fit, and its variance, can be related to tissue homogeneity. "Shadowing" is quantified by measuring mean midband fit values in two comparable regions of posterior tissues that are shadowed and not shadowed, respectively, by the lesion. The lesion attenuation coefficient is estimated from the difference between these mean values and the lesion thickness.

Initial results on biopsy-proven cases are promising. We are now investigating additional descriptors for lesion surfaces to quantify the "smoothness," "lobulation," and "invasiveness" categories that have proven useful in B-mode evaluations.